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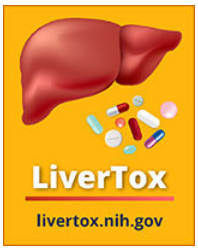

Pennyroyal Oil

Updated: March 28, 2020.

OVERVIEW

Introduction

Pennyroyal is an herbal extract or oil derived from leaves of the plant in the mint genus (Mentha pulegium) that was used in the past as an insect repellent and an abortifacient. When taken by mouth, pennyroyal oil is highly toxic and has been linked to several instances of toxic liver injury and death.

Background

Pennyroyal is derived from leaves of either Mentha pulegium or Hedeoma pulegoides, plants of the mint family that are native to Europe. Pennyroyal extract contains many components, but primarily contains the volatile oil pulegone and other monoterpenes. Pennyroyal has a strong fragrance similar to spearmint and was used for centuries to flavor food, wine and herbal teas. Pennyroyal extracts were also used as a traditional herb and folk remedy; a particular use was to stimulate menstruation and, in higher concentrations, to induce abortion. Pennyroyal tea and leaf extracts have been used without serious side effects. Pennyroyal oil, however, is highly toxic, and even small doses (one tablespoon, 15 mL) can cause syncope, seizures, coma, cardiopulmonary collapse, acute liver injury, renal insufficiency and multiorgan failure. Currently, pennyroyal oil is used in aromatherapy, as a bath additive and as an insect repellent, but is not recommended to be taken internally.

Hepatotoxicity

There have been many reported cases of pennyroyal oil toxicity, usually arising within a few hours of ingestion. Cardiovascular collapse with disseminated intravascular coagulation is the usual presentation, but some patients develop acute liver injury with marked elevations in serum aminotransferase levels and early signs of liver failure, such as prolongation of the prothrombin time and hepatic encephalopathy. The clinical pattern of liver injury is acute hepatic necrosis that, if severe, can lead to acute liver failure and death. Immunoallergic features are uncommon. Liver biopsy shows marked centrilobular necrosis which can resemble shock or acute acetaminophen overdose.

Likelihood score: B (likely cause of acute, clinically apparent liver injury).

Mechanism of Injury

Pennyroyal is clearly a direct cytotoxin. The toxic principal in pennyroyal oil appears to be pulegone which is converted by the cytochrome P450 system (CYP 1A2 and 2E1) to other hepatotoxins (menthofuran). Pulegone and its products deplete glutathionine levels and attempts at treating pennyroyal toxicity with N-acetyl cysteine

infusions are appropriate. Pennyroyal oil contains 85% pulegone and can cause acute multiorgan injury, including acute hepatic necrosis in experimental animals.

Outcome and Management

Pennyroyal oil is not recommended for oral intake, but cases of hepatotoxicity continue to be reported, largely from accidental or suicidal intake of the aromatic oil and rarely from its use as an abortifacient. Glutathionine has been shown to detoxify the toxic metabolites of pulegone and N-acetylcysteine should be administered in a manner similar to what is recommended for acetaminophen overdose. Cases were first reported more than 100 years ago; few have been published in the last two decades.

Drug Class: Herbal and Dietary Supplements

CASE REPORT

Case 1. Acute hepatitis due to pennyroyal oil.(1)

An 18 year old girl developed nausea, vomiting, abdominal pain, agitation and confusion starting a few hours after taking one ounce of pennyroyal oil in an attempt to induce abortion. She had drunk pennyroyal tea many times in the past to induce menstruation. She had no history of liver disease, alcohol abuse or risk factors for viral hepatitis, but had been depressed, and the ingestion of pennyroyal oil may have been a suicide attempt. On examination, vital signs were stable except for tachypnea. Laboratory tests including serum aminotransferase levels were normal except for a metabolic acidosis. Approximately 40 hours after admission, she was found to have evidence of disseminated intravascular coagulation with prothrombin time of 32 seconds, low fibrinogen levels and platelet count of 10,000/μL. At this point, serum enzyme levels were markedly elevated although serum bilirubin was only 1.2 mg/dL (Table). Over the next few days, the liver tests worsened and she developed progressive renal insufficiency, pulmonary failure and coma requiring intubation. She suffered recurrent cardiopulmonary arrest and multiorgan failure from which she died 7 days after the ingestion. Autopsy showed petechiae in multiple organs, pulmonary consolidation and massive centrilobular hepatic necrosis and rupture of the liver with 4.5 L of blood in the peritoneum.

Key Points

Medication:	Pennyroyal oil (one ounce)
Pattern:	Hepatocellular (R=110)
Severity:	5+ (jaundice, hospitalization, death from multiorgan and hepatic failure)
Latency:	Within 24 hours
Recovery:	None
Other medications:	None

Laboratory Values

Time After Ingestion	ALT (U/L)	AST (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
<4 hours	Normal	Normal	Normal	Normal	Acidosis
2 days		5,960	80	1.2	LDH 7960 U/L
3 days	4,400	10,160	93	6.1	Protime 19 sec
4 days	1,240	1,060		12.0	Creatinine 3.7 mg/dL
5 days		Cardiopulmonary arrest, resuscitated			

Table continued from previous page.

Time After Ingestion	ALT (U/L)	AST (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
7 days		Cardiopulmonary arrest, death			
Normal	**<40**	**<40**	**<130**	**<1.2**	

Comment

The tragic course and outcome of the pennyroyal oil poisoning resembled acetaminophen overdose, with acute hepatic necrosis arising two to three days after the ingestion of the herbal oil accompanied by renal failure, metabolic acidosis and generalized collapse. The finding of centrilobular necrosis on autopsy also resembles acetaminophen overdose, but is also compatible with acute ischemic necrosis. The hepatic rupture was perhaps due to the extensive hepatic necrosis and possibly the cardiopulmonary resuscitation efforts.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Pennyroyal Oil – Generic

DRUG CLASS

Herbal and Dietary Supplements

SUMMARY INFORMATION

Fact Sheet at MedlinePlus, NLM

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Pennyroyal	8007-44-1	Herbal mixture	Not applicable

CITED REFERENCE

1. Sullivan JB Jr, Rumack BH, Thomas H Jr, Peterson RG, Bryson P. Pennyroyal oil poisoning and hepatotoxicity. JAMA. 1979;242:2873–4. PubMed PMID: 513258.

ANNOTATED BIBLIOGRAPHY

References updated: 28 March 2020

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 731-4.

(Expert review of hepatotoxicity published in 1999; pennyroyal oil is discussed as an ostensible abortifacient that has toxicity that can be reproduced in experimental animals).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58.

(Review of hepatotoxicity of herbal and dietary supplements [HDS] mentions that pennyroyal hepatotoxicity may be due to depletion of glutathione by pulegone).

Pennyroyal. In, PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp. 639-40.

(Compilation of short monographs on herbal medications and dietary supplements).

Girling J. Poisoning by pennyroyal. Br Med J. 1887;1:1214.

(40 year old woman went into coma an hour after taking pennyroyal oil, responding to hypodermic injections of apomorphine and brandy).

Flynn EF. Poisoning by essence of pennyroyal. Br Med J. 1893;2:1270.

(A "small, delicate woman" took pennyroyal oil for abortion and developed agitation, fright and weakness, responding to emetics).

Allen WT. Note on a case of supposed poisoning by pennyroyal. Lancet. 1897;1(3841):1022–3.

(23 year old woman developed vomiting followed by collapse a few hours after swallowing a tablespoon of pennyroyal oil, dying 8 days after ingestion).

Braithwaite PF. A case of poisoning by pennyroyal: recovery. Br Med J. 1906;2:865.

(Young woman took half an ounce of essence of pennyroyal to induce menstruation and developed nausea, vomiting, confusion and stupor, responding to emetics).

Vallance WB. Pennyroyal poisoning: a fatal case. Lancet. 1955;269(6895):850–1. PubMed PMID: 13264630.

(24 year old woman developed fatigue and vomiting a few hours after taking pennyroyal oil to induce abortion and, failing that, underwent an abortion followed by excessive bleeding, fever and rash, with subsequent renal failure and death 10 days later; on autopsy, there was acute tubular necrosis, "the liver appeared relatively normal").

Early DF. Pennyroyal: a rare cause of epilepsy. Lancet. 1961;278(7202):580–1.

(23 year old woman had multiple seizures followed by an acute psychotic reaction after taking pennyroyal oil 3-4 times daily for 4 days, ultimately resolving completely; author quotes 3 previous reports of seizures following pennyroyal use).

Mack RB. "Boldly they rode ... into the mouth of hell". Pennyroyal oil toxicity. N C Med J. 1997;58:456–7. PubMed PMID: 9392962.

(Review of pennyroyal oil toxicity and suspected mechanism of injury and possible role of glutathione depletion).

Centers for Disease Control. Fatality and illness associated with consumption of pennyroyal oil–Colorado. MMWR Morb Mortal Wkly Rep. 1978;27:511–3.

(Three unrelated cases of women taking 0.25-1 ounce of pennyroyal oil in unsuccessful attempts to induce abortion; ages 18, 21 and 24 years, developing nausea, dizziness and paresthesias a few hours after ingestion, 2 recovering rapidly with normal liver tests, one developing acute liver failure and dying after 6 days, autopsy showing massive hepatic necrosis).

Sullivan JB Jr, Rumack BH, Thomas H Jr, Peterson RG, Bryson P. Pennyroyal oil poisoning and hepatotoxicity. JAMA. 1979;242:2873–4. PubMed PMID: 513258.

(Two cases of pennyroyal oil overdose in abortion attempts: 18 year old took one ounce of pennyroyal oil developed nausea and agitation, with progressive acidosis and hematemesis [bilirubin 1.8 mg/dL, AST 5960 U/L, LDH 7960 U/L, Alk P 80 U/L] in first few hours progressing to hepatic failure and cardiovascular collapse by day 6 [Case 1]; 22 year old woman developed dizziness after ingesting 10 mL of pennyroyal oil, but had normal

laboratory values and was discharged in 2 days; probably 2 of 3 cases which were also described in MMWR [1978]).

Gold J, Cates W Jr. Herbal abortifacients. JAMA. 1980;243:1365–6. PubMed PMID: 7359700.

(Editorial on Sullivan et al. [1979] from the CDC stating that this was the first report of a death after use of an abortifacient and it is unclear why herbal medicines are used for this purpose in view of the availability of legal abortions).

Gordon WP, Fort AJ, McMurtrey RJ, Gal J, Nelson SD. Hepatotoxicity and pulmonary toxicity of pennyroyal oil and its component terpenes in the mouse. Toxicol Appl Pharmacol. 1982;65:413–24. PubMed PMID: 7157374.

(In mice, (R)-(+)-pulegone [the major terpene in pennyroyal oil] is toxic to lung and liver, causing central necrosis and marked ALT elevations accompanied by glutathione depletion).

Buechel DW, Haverlah VC, Gardner ME. Pennyroyal oil ingestion: report of a case. J Am Osteopath Assoc. 1983;82:793–4. PubMed PMID: 6874446.

(20 year old woman took pennyroyal in tea for 2 weeks to induce menstruation and then 15 capsules at once to induce menstruation, developing nausea, weakness and syncope within hours, with normal liver tests, treated with N-acetylcysteine and recovering within 24 hours).

Bakerink JA, Gospe SM Jr, Dimand RJ, Eldridge MW. Multiple organ failure after ingestion of pennyroyal oil from herbal tea in two infants. Pediatrics. 1996;98:944–7. PubMed PMID: 8909490.

(Two cases of severe pennyroyal toxicity in infants, 8 week and 6 months old, who were treated with locally prepared mint tea for respiratory illness and developed metabolic acidosis, seizures and multiorgan failure [bilirubin 2.9 and 1.4 mg/dL, ALT 2856 and 2013 U/L, Alk P 307 U/L, LDH 9055 and 2231 U/L], one dying and one surviving with neurologic deficits; one tea was shown to contain pulegone).

Anderson IB, Mullen WH, Meeker JE. Khojasteh-BakhtSC, Oishi S, Nelson SD, Blanc PD. Pennyroyal toxicity: measurement of toxic metabolite levels in two cases and review of the literature. Ann Intern Med. 1996;124:726–34. PubMed PMID: 8633832.

(Four cases of pennyroyal toxicity; 24 year old woman took pennyroyal oil to induce abortion and developed nausea, syncope and cardiopulmonary arrest and later died of multiorgan failure [AST rising from 49 to 2672 U/L], autopsy showing centrilobular necrosis; 22 month old girl drank pennyroyal oil and was treated with gastric lavage and N-acetylcysteine within an hour and thereafter had no liver test abnormalities; two other cases had mild dizziness and gastrointestinal symptoms after pennyroyal tea ingestion).

Stedman C. Herbal hepatotoxicity. Semin Liver Dis. 2002;22:195–206. PubMed PMID: 12016550.

(Review and description of patterns of liver injury, including discussion of potential risk factors, and herb-drug interaction; pennyroyal oil is said to be widely available and used as an abortifacient as well as a pesticide and general herbal tonic).

Schiano TD. Hepatotoxicity and complementary and alternative medicines. Clin Liver Dis. 2003;7:453–73. PubMed PMID: 12879994.

(Comprehensive review of herbal associated hepatotoxicity, including pennyroyal oil which typically causes severe gastrointestinal upset and central nervous system effects within 1-2 hours of ingestion of 10 mL or more, hepatic dysfunction becomes prominent later).

Pittler MH, Ernest E. Systematic review: hepatotoxic events associated with herbal medicinal products. Aliment Pharmacol Ther. 2003;18:451–71. PubMed PMID: 12950418.

(Systematic review of published cases of hepatotoxicity due to herbal medications listing 52 case reports or case series, most common agents being celandine [3], chaparral [3], germander [8], Jin Bu Huan [3], kava [1], Ma Huang [3], pennyroyal oil [1], skullcap [2], Chinese herbs [9], valerian [1]).

Seeff LB. Herbal hepatotoxicity. Clin Liver Dis. 2007;11:577–96. PubMed PMID: 17723921.

(Review of herbal induced hepatotoxicity, including pennyroyal oil which is known to be hepatotoxic, although most cases of toxicity have gastrointestinal distress and central nervous system dysfunction).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135:1924–34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 9% of cases were attributed to herbal medications, but no case was attributed to pennyroyal oil alone or in combination with other agents).

García-Cortés M, Borraz Y, Lucena MI, Peláez G, Salmerón J, Diago M, Martínez-Sierra MC, et al. Rev Esp Enferm Dig. 2008;100:688–95. [Liver injury induced by "natural remedies": an analysis of cases submitted to the Spanish Liver Toxicity Registry]. Spanish. PubMed PMID: 19159172.

(Among 521 cases of drug induced liver injury submitted to Spanish registry, 13 [2%] were due to herbals, none due to pennyroyal oil).

Navarro VJ. Herbal and dietary supplement hepatotoxicity. Semin Liver Dis. 2009;29:373–82. PubMed PMID: 19826971.

(Overview of the regulatory environment, clinical patterns, and future directions in research with HDS; pennyroyal oil is listed as a potential hepatotoxin but not specifically discussed).

Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int. 2012;32:1543–56. PubMed PMID: 22928722.

(A systematic compilation of all publications on the hepatotoxicity of specific herbals identified 185 publications on 60 different herbs, herbal drugs and supplements including four publications on pennyroyal).

Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. Aliment Pharmacol Ther. 2013;37:3–17. PubMed PMID: 23121117.

(Systematic review of literature on HDS associated liver injury mentions that pennyroyal oil can cause severe central nervous system effects, hepatic necrosis and multiorgan failure).

Gordon P, Khojasteh SC. A decades-long investigation of acute metabolism-based hepatotoxicity by herbal constituents: a case study of pennyroyal oil. Drug Metab Rev. 2015;47:12–20. PubMed PMID: 25512112.

(Chemical component analysis and in vivo testing of pennyroyal oil indicates that the major cytotoxin is the terpene pulegone which constitutes ~80% of the oil and which is metabolized by CYP 2E1 to menthofuran, which is highly hepatoxic in rodent models).

Navarro VJ, Seeff LB. Liver injury induced by herbal complementary and alternative medicine. Clin Liver Dis. 2013;17:715–35. PubMed PMID: 24099027.

(Review of HDS induced liver injury including regulatory problems, difficulties in diagnosis and causality assessment; mentions that pennyroyal has long been known to be toxic and capable of causing acute hepatic necrosis in a pattern similar to acetaminophen, the toxic components being pulegone and menthofuran).

Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology. 2014;60:1399–408. PubMed PMID: 25043597.

(Among 85 cases of HDS associated liver injury [not due to anabolic steroids] enrolled in a US prospective study between 2004 and 2013, none were attributed to pennyroyal).

García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by dietary supplements: A tabular listing and clinical characteristics. Int J Mol Sci. 2016;17:537. PubMed PMID: 27070596.

(Listing of published cases of liver injury from HDS products, but does not list those attributed to pennyroyal).

Brown AC. Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series. Food Chem Toxicol 2017; 107 (Pt A): 472-501.

(Description of an online compendium of cases of liver toxicity attributed to HDS products, lists pennyroyal [mentha puleium] as capable of causing rapid onset of acute hepatic necrosis, particularly in children and pregnant women).